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Supramolecular glycopolymers: How carbohydrates matter in structure, dynamics, and function

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Abstract

Supramolecular glycopolymers exhibiting inherent dynamicity, tunability, and adaptivity allow us to arrive at a deeper understanding of multivalent carbohydrate–carbohydrate interactions and carbohydrate–protein interactions, both being essential to key biological events. The impacts of the carbohydrate segments in these supramolecular glycopolymers towards their structure, dynamics, and function as biomaterials are addressed in this minireview. Bottlenecks and challenges are discussed, and we speculate about possible future directions.

Addresses

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Keywords

Supramolecular glycopolymers, Non-covalent interactions, Dynamics, Biomaterials.

Introduction

Based on comprehensive fundamental understanding, one-dimensional supramolecular polymers — polymers held together with directional and reversible non-covalent interactions — have shown great potential for applications in catalysis, electronics, and medicine in the last two decades [1,2]. The modular approach of supramolecular polymers opens endless possibilities to arrive

at functional biomaterials, while the dynamic nature of these polymers provides them with the highly desirable adaptive and responsive properties. One of the most successful examples is the peptide amphiphiles developed by the Stupp group, that have been exploited in tissue engineering and regenerative medicine, making use of both the dynamic and modular features [3,4].

Meanwhile, the investigation of glycopolymers — synthetic macromolecules with carbohydrates as pendent groups — became a fascinating topic since the late 1980s, mainly promoted by the discovery of the multivalent carbohydrate–protein interactions (CPIs) which are essential throughout most of the biological events [5–8]. Moreover, the development of a variety of living polymerization strategies, as well as the highly efficient click reactions, made these macromolecular systems versatile and consequently widely applied [9]. The macromolecular glycopolymers developed to date are significantly simplified in their structure when compared to their natural analogues, for example, the glycoproteins, glycolipids, and proteoglycans. Yet the manifold presentation of carbohydrates nicely mimics the multivalent display of carbohydrates found in glycans, providing an ideal model to gain a deeper understanding of multivalent carbohydrate–carbohydrate interactions (CCIs) as well as the CPIs. However, there are some limitations of these tailor-made covalently formed glycopolymers, such as (1) a relatively static composition with restricted adaptivity, which increases the conformational entropy during binding process, and (2) often contain a limited chain length compared to natural glycans, making it difficult to investigate long-range interactions [10]. In this regard, supramolecular glycopolymers (Figure 1), exhibiting inherent dynamicity and adaptivity, serve as promising candidates to tackle some of these challenges, while several micrometer-long polymers can be prepared. The spatial rearrangement could easily be adopted through dynamic monomer exchange within the supramolecular polymers to promote binding events [11,12]. Control over polymer length from nano-to micrometers has been achieved through, for instance, tuning the degree of crystallinity [13], and/or copolymerization [14].

Through the years, much effort has been devoted to fabricating supramolecular glycopolymers as highlighted in excellent review articles [10,15–17]. Interestingly, most of these polymers are classified according to their

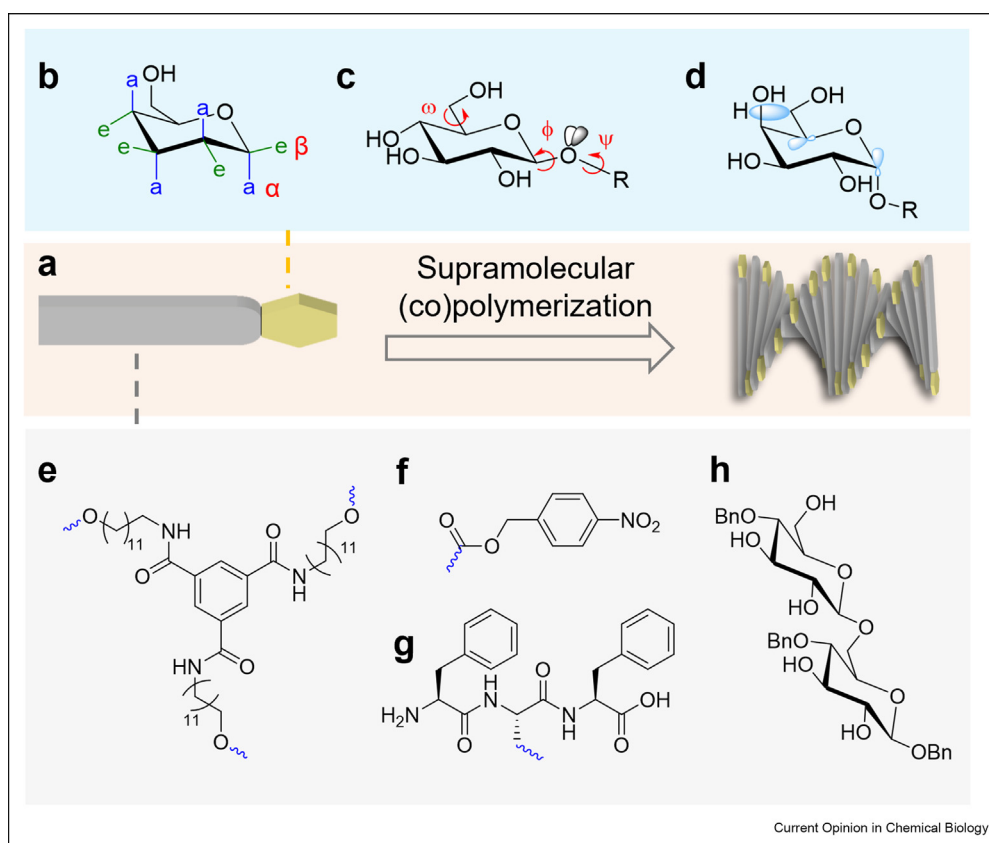
hydrophobic core, such as peptides, aromatic structures, nucleosides/nucleotides, C3-symmetrical discotic units, and aliphatic chains, with the carbohydrates simply serving as hydrophilic segment (Figure 1). However, in these studies the key features of carbohydrates, including CCIs, are typically overlooked. In this mini-review, we focus on the contributions of the carbohydrate units to the structure, dynamics, and function of the resulting supramolecular glycopolymers, followed by a brief discussion concerning the bottlenecks and challenges within this field.

Structure diversity and non-covalent interactions of carbohydrates

Carbohydrates exhibit a tremendous structural diversity and complexity in contrast to proteins and DNA [18], mainly arising from the multiple stereocenters, conformations (axial or equatorial), dihedral angles and stereo-electronic effects (Figure 1b–d), even within monosaccharides, while they can contain further modifications

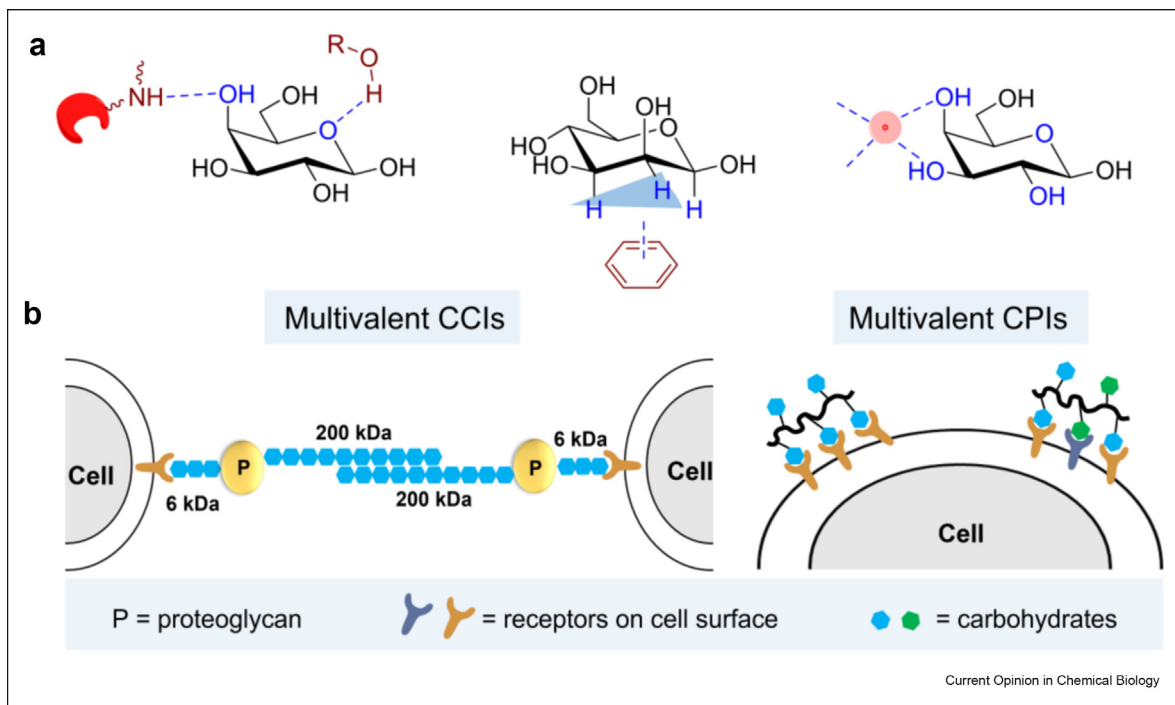
such as sulfation, methylation, and phosphorylation [19]. The non-covalent interactions (hydrogen bonding, CH– π interaction and coordination to, for example, calcium ions — Figure 2a, from left to right, respectively), originating from the polyol and the furano/pyranose motifs of carbohydrates, dictate the formation of CCIs and CPIs (Figure 2b, left and right, respectively) [20]. As monovalent carbohydrate–carbohydrate or carbohydrate–protein interactions are extremely weak ($K_D = 10^{-3}$ M), cooperativity with multiple carbohydrates is adopted to enable strong, reversible, and highly selective interactions in biological systems [5,21]. For instance, the entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is orchestrated by cooperative binding between trimeric spike glycoproteins and multiple dimeric angiotensin-converting enzyme-2 receptors at virion–cell interfaces [22]. Thus, neutralization or prevention of infection has been achieved through receptor binding competition using multivalent nanobodies [23,24].

Figure 1



Schematic supramolecular (co)polymerization (a) to afford a supramolecular glycopolymer, with the carbohydrate diversity addressed in the above blue panel (b–d) and representative chemical structures of supramolecular glycopolymers in the below grey panel (e–h). The structural diversity of carbohydrates is determined by (1) each hydroxyl group position that can be in axial (a) or equatorial (e) orientation (b), (2) three dihedral angles (ϕ , ψ , ω , c) and (3) the stereo-electronic effects (d). The hydrophilic and hydrophobic domains can be present in separate segments of the supramolecular monomers (e–g) but can also be intermixed as illustrated by the amphiphilic disaccharide with benzoyl protecting groups (h). The blue wavy bond represents the connection to the carbohydrate segment (e–g).

Figure 2



Overview of carbohydrate interactions and the resulting multivalent CCIs and CPIs. (a) Carbohydrate interactions, including hydrogen bonding, CH- π interactions with aromatic amino acid side chains, and coordination to ions, such as Ca²⁺. (b) Multivalent CCIs and CPIs occurring on the cell surface.

Control over structures

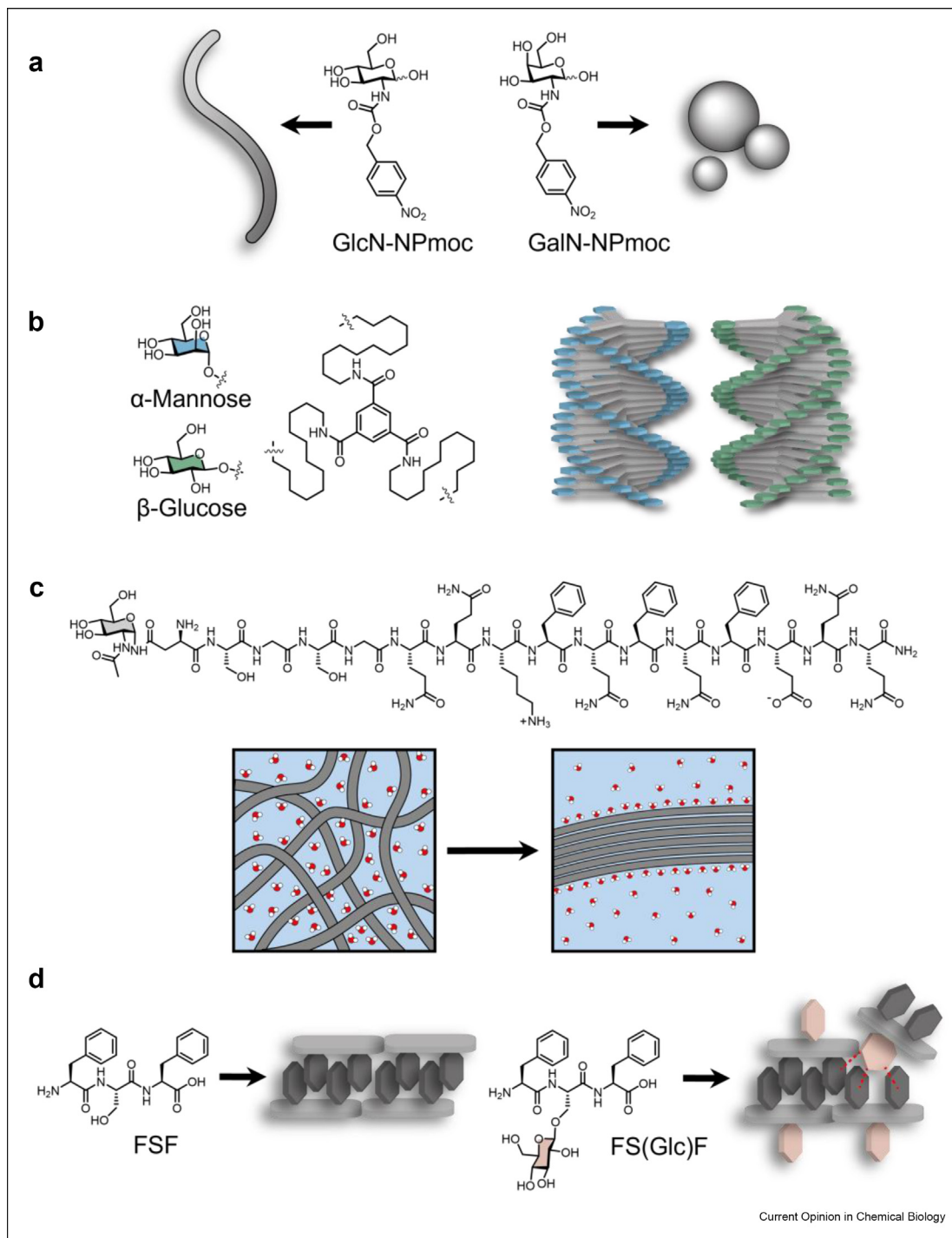
The carbohydrates' structural diversity along with its complex non-covalent interactions, influences the inner molecular packing, nanoscopic morphology, the helicity, and hierarchical order of the resulting supramolecular glycopolymers at different length scales. In this paragraph, the three major aspects will be discussed.

The molecular packing and subsequent morphology: In supramolecular polymerization, the design of the monomers is crucial. If there exists an imbalance in the hydrophilic/hydrophobic ratio, the monomers are unable to self-assemble into ordered structures, yet forming spherical micelles or precipitations instead. Small molecular differences, as little as the epimerization (*i.e.* change in configuration of only one stereogenic center) within carbohydrates, can already result in different molecular packing modes, hence influencing CCIs, and the subsequent overall morphology and length of the supramolecular glycopolymers. A glucosamine-based monomer possessing a 4-nitrophenylmethoxycarbonyl (NPmoc, Figure 1f) group linked through the amino group at the C2 position stacked into one-dimensional columnar structures, stabilized by hydrogen bonding interactions between neighboring C2-amide groups (GlcN-NPmoc, Figure 3a) [27]. However, its epimer at the C4 position, galactosamine-NPmoc, formed small spherical structures instead, owing to the formation of intermolecular hydrogen bonding of C4-OH and

C3-OH groups. The latter prevents hydrogen bonding occurring between the neighboring C2-amide groups. The effect of the glycosidic stereochemistry (α vs. β) was evaluated utilizing 18 disulfide linked dimeric glycopeptides bearing varied monosaccharides [28]. When the glycan contained an axial hydroxyl (*e.g.* galactose and mannose), the α -anomer showed gelation, whereas the β -anomer precipitated in phosphate buffer. This is due to a difference in carbohydrate-aromatic — CH- π bonding — between the carbohydrate and the tyrosine's aromatic ring of the peptide. Moreover, the epimerization of the C4-OH in lactose to cellobiose resulted in the transition from self-assembled nanofibers to thick nanoribbons, underpinning the importance of stereochemistry next to the type of glycosidic linkage [29].

Achieving control over the nanoscopic morphology was also successfully demonstrated by tuning the length of supramolecular glycopolymers through the formation or cleavage of glycosidic linkages. As such, Chen *et al.* utilized glycosyltransferases to promote glycosylation reactions on glucuronic acid-based glycopeptide fibers [30]. The glycosylation of *N*-acetyl-glucosamine or -galactosamine onto peripheral glucuronic acids transformed the polymer length gradually from micrometer to nanometers, and eventually to spherical nanoparticles over time. The addition of the newly introduced hydrophilic monosaccharides disrupted the hydrophilic/hydrophobic balance and with that the CCIs, thus

Figure 3



The effect of the carbohydrate moiety in selected supramolecular glycopolymer assembly. **(a)** GlcN-Pmoc assembled into fibrous structures whereas its epimer, GalN-Pmoc formed spherical structures instead. **(b)** BTA- α -mannose assembled into fibers with opposite helicity as BTA- β -glucose. **(c)** *N*-Acetylglucosamine peptide amphiphile formed hierarchical assemblies driven by macromolecular crowding. **(d)** Tripeptide FSF self-assembles by π - π stacking between neighboring phenylalanine amino acids, however, upon functionalizing the central amino acid with glucose, to obtain FS(Glc)F, CH- π interactions between the glucose and aromatic rings of the phenylalanines are formed (red dashed lines) thereby affecting the packing order and dynamics.

resulting in a morphological transition. Inversely, β -galactosidase was able to cleave the β -linked terminal galactosyl residues from glyconucleo-bolaamphiphile [31], diphenylalanine-based glycopeptides [14], and urea-based glycoconjugates [32], reducing the hydrophilicity and hence, instructing supramolecular polymerization. Having such control over the nanoscopic morphology opens avenues for the development of novel therapeutic biomaterials for example for cancer therapy such as releasing drugs from scaffolds. Not only the CCIs, and hence polymerization and depolymerization, within synthetic structures can be regulated in this manner, also arguably, interactions with native biomolecules in cellular environments. By switching between the monomeric state, exhibiting low binding, and the aggregated state, displaying multivalency and high binding strengths, downstream signaling pathways could be switched on and off.

The helicity: The inherent chirality of the carbohydrate segment allows for a direct transfer of asymmetry from the molecular level to the microscopic level, which is generally expressed as supramolecular helicity, and thereby enables the ability to control handedness in macromolecular assemblies. Delbianco et al. designed two enantiomeric phenyl functionalized disaccharides, based on either D-glucose (Figure 1h) or L-glucose [25]. They showed that the D-glucose disaccharide self-assembled into highly crystalline left-handed helical fibers, while the enantiomeric disaccharide assembled from L-glucose leveraged right-handed fibers, while the racemic mixture containing both disaccharides resulted in flat lamellae. The type of glycosidic linker (α vs. β) along with the orientation of OH groups also biased supramolecular chirality in a glucose and mannose functionalized benzene-1,3,5-tricarboxamides (BTA) system (Figure 1e) [26]. Specific Cotton bands were observed with opposite signs in the circular dichroism (CD) spectra when comparing glucose, attached via a β glycosidic linkage, with the α -mannose (Figure 3b). Noteworthy is the relative low CD signal of these glycopolymers in aqueous medium compared to the helical supramolecular polymers in organic media of a variety of structures. This is indicative for a limited amplification of molecular asymmetry to macromolecular helicity, which most probably arises from the blocky and/or less cooperative CCIs rather than continuous CCIs throughout the glycopolymer. Although in nature most macromolecular assemblies occur as left-handed, the ability to switch between helicities allows one to control; cellular binding, which is typically higher on left-handed structures as compared to right-handed; *in vivo* circulation times, due to reduced protease recognition on right-handed helices, hence lower clearance; and multivalent presentation of carbohydrates with a controlled lateral spacing and pitch to ensure optimal CPI binding due to an induced fit.

The hierarchical assembly: Gaining control over the hierarchical assembly across several length scales enables enhanced mechanical properties and more complex functionalities. In attempts to reach this, anisotropic alignment of supramolecular glycopolymers was achieved upon *N*-acetylglucosamine functionalized peptides in a molecular crowded environment (Figure 3c) [33]. In contrast to non-glycosylated nanofibers, the dense carbohydrate presentation facilitates the nanofiber lateral association and alignment, yielding micrometers thick bundles, due to weak inter-fiber CCIs. However, in some cases the hierarchical assembly is undesired, such as in the formation of amyloid- β fibrils that deposit into the amyloid plaques linked with Alzheimer's disease. To reduce amyloid fibril formation, *O*-glycosylation of amyloid- β peptides with mono-, di-, and trisaccharide was shown to dramatically reduce the fibril formation, with the trisaccharide showing the most significant modulatory effect [34]. Hierarchical aggregation was abolished by increased hydration due to the glycosylation causing enhanced steric hindrance. Although still in its infancy, the ability to control the anisotropic direction, rather than random isotropic arrangements — which can be achieved with external triggers such as light and magnetism — of these hierarchical assemblies is expected to be able to direct cell growth, polarization and multi-cellular tissue organization, permitting the construction of artificial grafts and organs in a dish with the correct architecture, organization and function.

Control over dynamics

The inherent dynamic property of supramolecular polymers is without doubt the most fascinating and yet far more elusive property that allows readjustments for optimal functional group presentation [1,35]. Experimental studies [11,36,37] and molecular simulations [38] at diverse length- and timescales provide us with opportunities to gain deeper insights and this allows us to gain better control over its conformational dynamics, its adaptivity, and hence its subsequent function. To this end, the internal dynamics of the BTA (Figure 4, dynamics panel for a cartoon representation) has been investigated in detail with and without fluorescent probes. As slight modifications, such as attached fluorescent dyes, can have a tremendous effect on the internal dynamics of supramolecular polymers, hydrogen/deuterium exchange-mass spectrometry (HDX-MS) was introduced to investigate the behavior of the true monomers, rather than dye functionalized monomers. It was discovered that BTA dynamics strongly relies on the size of the hydrophobic pocket [36]. The longer the hydrophobic aliphatic chain, the better it shields intermolecular hydrogen bonds from water, thereof leverages a stable structure compared to the shorter counterparts. When the hydrophilic part was modified from tetraethylene glycol to *O*- α -mannose, a slower monomer

exchange was revealed, arising from strong CCI between the mannosylated moieties. In contrary, *O*- β -glucose [26] and triazine- β -glucose [39] moieties showed significant higher initial monomer exchange rates, despite of similar fibrous morphology resemblance. This suggests that the glycosidic linkage and the C2–OH orientation influence the final CCIs and degree of hydration, which in turn affects the molecular packing and the internal dynamics. A similar trend has been observed in a series of bola-amphiphilic glycolipid-type supramolecular polymers, in which the α -anomer-bearing glycolipids showed a higher stability, hence exhibiting slower exchange dynamics, than their β -anomer counterparts [40].

Exploring the impacts of CH– π interactions on the internal dynamic properties in supramolecular polymers allows for a deeper understanding of CPIs [41,42]. To this end, Ulijn et al. introduced glycosylation sites in the middle of two tripeptides as minimalistic *O*-glycoprotein mimics (Figure 1g, and Figure 3d) [43]. The CH– π interactions that were formed between the hydrophilic glucose segments and aromatic phenylalanine amino acids, affected the n – π and π – π interactions of the aromatic stacking. As such, packing disorder and dynamics were subsequently enhanced within the assembled structures. The dynamic profile of the supramolecular biomaterial, however, needs to be tuned according to the desired application, as every cell type requires a distinct environment, and cellular events occur at specific time scales, ranging from nanoseconds to sometimes hours. As such, being able to control dynamic properties can regulate multivalent displays in relevant time scales, thereby switching signaling pathways on and off, and the possibility to program in feedback loops.

Supramolecular glycopolymers as functional biomaterials

Essential to the success of a supramolecular glycopolymer is the ability to engage in multivalent CCIs and CPIs. The power of multivalency arises from the ability to rearrange its conformation to yield an induced fit and hence tight multivalent binding by cooperativity. Reaching such control in synthetic mimics therefore requires control over the internal dynamic property of supramolecular polymers, that is, the ability of the monomers to rearrange within the supramolecular polymer backbone for optimal epitope presentation, clustering and hence cooperative binding. Although a detailed fundamental understanding of the “structure-dynamics-function” relationship in supramolecular glycopolymers is lacking, a wide variety of biomedical applications, including in immunotherapy [44], drug delivery [45,46], and regenerative medicine [47], have already been explored.

Supramolecular glycopolymeric hydrogels are promising candidates for mimicking the highly glycosylated microenvironment of extracellular matrix [48]. The hydrophilic nature of carbohydrates allows the immobilization of water, hence providing swelling and gelling properties, and enables resistance to compressive forces. It is also able to form a hydration shell, thereby encapsulating and protecting, for example, labile growth factors from (enzymatic) degradation. Next to physical properties, specific carbohydrate moieties are involved as biomolecular cues for improving cell attachment [49], growth [50], and differentiation [51,52] occurring through multivalent CPIs. Moreover, carbohydrates typically display a viscoelastic property that arises from the non-covalent interactions of physical crosslinks and entanglements. A material with viscoelastic properties, as investigated in detail and demonstrated for alginate, has been shown to exhibit stress relaxation and creep properties [53]. Exhibiting these properties, is even more important than just mechanical properties, as it has been shown that viscoelastic hydrogels improve the (stem) cell fate in both 2D as in 3D cell culture environments due to the ability to dissipate strain and allow local remodeling, thereby facilitating cell spreading, proliferation, and differentiation. Enriching these viscoelastic materials with peptides and carbohydrate moieties that can synergistically bind cells at relevant time scales and across several length scales is envisioned to be increasingly important for biomedical applications.

Bottlenecks and challenges

Although significant steps towards fabricating supramolecular glycopolymers have been made, the understanding and utilization in both fundamental properties and applications are still in its infancy. In the following section we highlight some challenges and discuss where supramolecular glycopolymers can be improved.

As disclosed above, all the examples are still relying on simple mono-, di-, or trisaccharide groups. More complex oligosaccharides and polysaccharides found in native carbohydrates are urgently needed. However, although advanced automated synthesis of oligosaccharides is developing, it is still far from being simple to fabricate polysaccharide chains with similar regioselectivity and configuration control as nature does and apply them as sidechains for supramolecular glycopolymers [17]. Breakthroughs from carbohydrate chemical and chemoenzymatic synthesis are highly demanded.

The carbohydrate structure diversity is a double-edged sword that provides opportunity to tune the structures and dynamics while in the meantime, this diversity in structure makes it extremely difficult to predict the assembled morphology *a priori*. To date, the construction of the supramolecular glycopolymers is still mainly

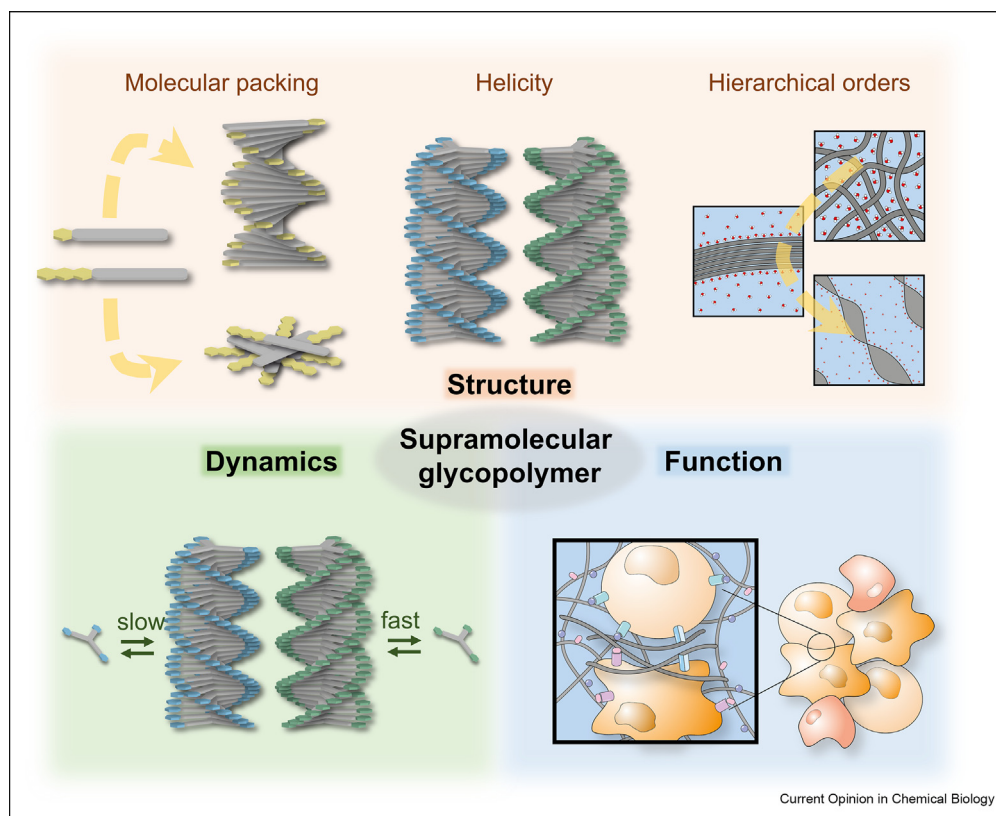
based on trial-and-error methods to find the sweet spot of a well-balanced hydrophilic/hydrophobic ratio. Sophisticated computer simulations and machine learning methods can help to find trends in existing data. With these trends, hopefully reliably predictions can be made for supramolecular glycopolymers' structure-dynamics-function relationships of new molecules by determining 1) the amphiphilic ratio, hydrogen bonding modes originating from the different carbohydrate building blocks and glycosidic bonds; 2) the correlations between the molecular structure and the hierarchical morphologies at both the macroscopic and microscopic scale and ultimately 3) predicting native bio-macromolecular binding [12].

Gaining a molecular level understanding of both carbohydrate-carbohydrate interactions (CCIs) and carbohydrate-protein interactions (CPIs) is still challenging due to the lack of suitable and powerful analytical techniques that can visualize single elements in the highly complex (that might involve multiple components) and dynamic environment. Recently, Albertazzi *et al.* introduced a point accumulation in nanoscale topography super-resolution microscopy method and successfully captured weak glycan-lectin

interactions at the single-molecule level in living cells [54]. Delbianco *et al.* utilized electron tomography and electron diffraction methods to study the CCIs [55]. These are great examples yet more advanced and sophisticated tools are still required.

Translating the obtained fundamental understanding towards achieving (biomedical) applications requires linking molecular design principles and nanoscopic interactions to desirable (cellular) responses. For instance, by tuning the interaction strength with therapeutic agents, such as drugs and growth factors, allows one to utilize the supramolecular glycopolymeric material as a therapeutic depot, thereby protecting, releasing, and delivering at relevant time scales [56]. Despite that the inherent viscoelastic properties of glycopolymers would be able to act as a matrix and support cell and tissue culture, optimization of the design parameters, including their dynamics, structure, and functionality, is expected to be essential to further steer and match the desired response. Moving away from simple matrices, requires the use of multiple components, hence a multicomponent system displaying numerous distinct and multivalent functional cues, that can function across several length- and timescales enriched with spatial

Figure 4



Overview of the impacts of carbohydrate parts in supramolecular glycopolymers towards the structure, dynamics, and function as biomaterials.

control. Moreover, including non-Newtonian behavior, such as shear-thinning for injectability [57] and strain-stiffening [58] for load-bearing mechanical support is speculated to be increasingly important as well.

Conclusion

In this minireview, the impacts of carbohydrates towards the assembly, structure, dynamics, and function of the formed supramolecular glycopolymers are addressed (Figure 4). The stereochemistry, type of glycosidic linkage and hydrophilic/hydrophobic balance play significant roles thereby affecting multivalent carbohydrate–carbohydrate interactions (CCIs) and carbohydrate–protein interactions (CPIs). The field is highly interdisciplinary with indispensable contributions from chemistry, biology, and physics, and could benefit from complementary fundamental insights into advanced computational simulations and machine learning to both predict the structure-dynamics-function relationship *a priori* as well as understand the spatial molecular interactions. With combining knowledge and breakthroughs across fields, more precise supramolecular glycopolymer structures with tunable dynamic and (hierarchical) assembly properties could be achieved, which will further support in elucidating biological events in detail and creating more sophisticated biomaterials for a wide variety of biomedical applications in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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